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Cerebellar atrophy and changes in cytokines associated with the CACNA1A R583Q mutation in a Russian familial hemiplegic migraine type 1 family

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Abstract

© 2017 Khaiboullina, Mendelevich, Shigapova, Shagimardanova, Gazizova, Nikitin, Martynova, Davidyuk, Bogdanov, Gusev, van den Maagdenberg, Giniatullin and Rizvanov. Background: Immune mechanisms recently emerged as important contributors to migraine pathology with cytokines affecting neuronal excitation. Therefore, elucidating the profile of cytokines activated in various forms of migraine, including those with a known genetic cause, can help in diagnostic and therapeutic approaches. Methods: Here we (i) performed exome sequencing to identify the causal gene mutation and (ii) measured, using Bio-Plex technology, 22 cytokines in serum of patients with familial migraine (two with hemiplegic migraine and two with migraine with aura) from a Russian family that ethnically belongs to the Tatar population. MRI scanning was used to assess cerebellar atrophy associated with migraine in mutation carriers. Results: Whole-exome sequencing revealed the R583Q missense mutation in the CACNA1A gene in the two patients with hemiplegic migraine and cerebellar ataxia with atrophy, confirming a FHM1 disorder. Two further patients did not have the mutation and suffered from migraine with aura. Elevated serum levels of pro-inflammatory and pro-nociceptive IL-6 and IL-18 were found in all four patients (compared to a reference panel), whereas pro-apoptotic SCGF-β and TRAIL were higher only in the patients with the FHM1 mutation. Also, cytokines CXCL1, HGF, LIF, and MIF were found particularly high in the two mutation carriers, suggesting a possible role of vascular impairment and neuroinflammation in disease pathogenesis. Notably, some “algesic” cytokines, such as β-NGF and TNFβ, remained unchanged or even were down-regulated. Conclusion: We present a detailed genetic, neurological, and biochemical characterization of a small Russian FHM1 family and revealed evidence for higher levels of specific cytokines in migraine patients that support migraine-associated neuroinflammation in the pathology of migraine.

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Keywords

Cytokines, FHM1, Inflammation, Migraine, Nociception

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